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EXAMINER
TATE, CHRISTOPHER ROBIN

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/888,997	Applicant(s) Aylward
	Examiner Christopher Tate	Art Unit 1654

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 6, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *33-95* is/are pending in the application.

4a) Of the above, claim(s) *35-73, 78-81, and 93-95* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *33, 34, 74-77, and 82-92* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of Group I, claims 33-77 and 82-92, in Paper No. 8 is acknowledged. The traversal is on the ground(s) that Groups I -III are not independent and distinct, including since the subject matter of all of the claims is related to the administration to a subject of an effective amount of at least one compound derived from the sap of *Euphorbia*. This is not found persuasive for the reasons set forth in the previous Office action - i.e., the method of Group I require the administration of an effective amount of one active compound (from among numerous distinct compounds recited therein), whereas the method of Group II requires the administration of an effective amount of a combination of at least two bioactive compounds (from among numerous distinct compounds recited therein). Also, the two or more bioactive compounds administered in the Group II method (from among the numerous compounds recited therein) do not necessarily include the singular compound of Group I. Further, the method of Group III is drawn to the administration of an undefined compound (e.g., plant extract) which does not necessarily include any of the compounds of Groups I or II and, further, is directed to a different functional effect than that of Groups I and II. One would not have to practice the various methods at the same time to practice just one method alone. In addition, the search for each of the invention groups is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for

patentability is different in each case. Thus, it would be an undue burden to examine both of the inventive groups in one application.

The Restriction requirement is still deemed proper and is therefore made FINAL.

In addition, Applicant's election with traverse of the chemical compound species Group D - i.e., a method of stimulating the immune system using an angeloyl-substituted ingenane compound or derivative or salt thereof. Applicant argues (and thus apparently admit) that the various compounds are not patentably distinct. As noted in the previous Office action, should applicant traverse on the ground that the species are not patentably distinct, then if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention. However, without a clear admission by Applicant that the various chemical compounds of Groups A-D are not patentably distinct, the election of species requirement stands for the reasons of record - i.e., the chemical compounds of species A-D are mutually exclusive (and thus different and distinct), each from the other. Accordingly, a reference which would anticipate the invention with respect to administering one chemical species (for stimulating immunity) would not necessarily anticipate or even make obvious administering another chemical species therefor. Thus, it would be an undue burden to examine the four different and distinct chemical species of A-D within in a method of treating cancer in one application.

The Election of Species requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 35-73, 78-81, and 93-95 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 33, 34, 74-77, and 82-92 are presented for examination on the merits.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

With respect to the elected invention, claims 33, 34, 74-89, and 94-99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulating the immune system of a subject via administering an effective amount of an angeloyl-substituted ingenane or salt thereof obtained from one of the three demonstrated/disclosed *Euphorbia* plant species (i.e., *E. peplus, E. drummondii* and *E. hirta*), does not reasonably provide enablement for stimulating the immune system of a subject using any and all compounds - including any and all derivatives of angeloyl-substituted ingenane - obtained from any and all *Euphorbia* plant species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

With respect to the elected invention, Applicant has reasonably demonstrated and disclosed that angeloyl-substituted ingenane obtained from *E. peplus, E. drummondii* and/or *E. hirta* can be used in the manner instantly claimed for stimulating immunity *in vivo*. However, the claims encompass the use of any and all compounds - including any and all derivatives of angeloyl-substituted ingenane - from any and all *Euphorbia* plant species which is clearly beyond the scope of the instantly demonstrated/disclosed invention, especially given that many of the active principles (compounds) obtained from numerous *Euphorbia* plant species are admittedly well known to actually have harmful carcinogenic activity including promoting tumor growth (see, e.g., pages 5 and 9 of the instant specification) in part due to their well known activity as an irritant (see, e.g., the discussion on pages 2-9 in the June 2001 Office action of parent Application No. 09/486,199 with respect to this well known tumor-inducing activity of compounds and/or extracts from various *Euphorbia* plant species).

Accordingly, with respect to the elected invention, it would take undue experimentation without a reasonable expectation of success for one of skill in the art to stimulate the immune system of a subject via administering an effective amount of a compound - including any and all derivatives of angeloyl-substituted ingenane - obtained from any and all *Euphorbia* plant species, other than administering an effective amount of an angeloyl-substituted ingenane or an active derivative of angeloyl-substituted ingenane which exhibits the same activity of the angeloyl-substituted ingenane, which is obtained from one of the three demonstrated/disclosed *Euphorbia* species - *E. peplus, E. drummondii* and *E. hirta*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 33, 34, 74-77, and 82-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 recites the limitation "the subject" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 is rendered vague and indefinite by the phrase "is capable of inhibiting" (step c). It is unclear by this phrase if the compound does or does not inhibit growth of at least one of the recited cell lines - e.g., is it only capable of inhibiting one or more cell lines under certain conditions and not others and, if so, what conditions are applicable? It is suggested that this phrase be amended to recite --inhibits-- to clearly define this limitation.

Claims 74-77 are rendered vague and indefinite by the phrase "a angeloyl-substituted derivative". One would not know how to interpret the metes and bounds of the term "derivative" within this phrase. For example, a derivative of a chemical compound may be closely patterned after the subject chemical compound or may be loosely patterned after the subject chemical compound such that it may bear little or no resemblance or form recognizable as the subject chemical compound which may be chemically and/or biologically unrelated in function or form to the subject chemical compound. It is suggested that this phrase be amended in claim 74 so as to define the claimed derivative as an active derivative of angeloyl-substituted ingenane which

exhibits the same activity of the angeloyl-substituted ingenane - such as recited in claim 1 U.S. Patent No. 6,432,452 (parent application 09/486,199).

Claim 74 is also rendered vague and indefinite by the phrase "wherein the compound comprises a composition selected from" (lines 1-2) because the recited compounds thereafter are not compositions, per se, they are compounds. It is suggested that this phrase be amended to recite --wherein the compound is selected from--.

Claims 83-90 are rendered vague and indefinite by the phrase "capable of" (line 1 of each) - i.e., it is unclear if the claimed functional effect occurs or not - e.g. is the compound capable of providing the claimed functional effect under some working conditions but not others and, if so, what are the working conditions? It is suggested that these claims be amended to recite --wherein the compound inhibits or retards-- (claim 83); --wherein the compound induces-- (claims 84-88); --wherein the compound recruits-- (claim 89, and possible claim 90? - it appears that the term "recruiting" is inadvertently missing from claim 90, which also causes confusion as to its overall meaning) to clarify this ambiguity.

Claim 94 is rendered vague and indefinite by the phrase "wherein the compound further comprises a beta-alanine betaine or a hydroxy-dimethyl proline" because a compound, per se, would not reasonably be definable as also containing these agents therein. It is suggested that this phrase be expanded to appropriately recite the limitations of claim 98 in conjunction with these carrier agents.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Please note that the claims have been examined over the art below insofar as they read upon the claimed method of administering the elected chemical species.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33, 34, 74-77, and 83-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Zayed et al. (J. Cancer Res. Clin. Oncol., 1998) or by Abo (Fitoterapia, 1988), with evidence provided by Benjamini et al. (Immunology - A Short Course, 1988).

A method of stimulating the immune system via administering to a subject a compound comprising an angeloyl-substituted ingenane, an angeloyl-substituted ingenane derivative, and/or pharmaceutically acceptable salts thereof is apparently claimed.

Zayed et al. teach administering a compound comprising one of various angeloyl-substituted ingenane compounds and derivatives thereof to goats, as well as to mouse ears which are administered within a milk extract or separately. Abo discloses adminstering an angeloyl-substituted ingenane compound to mouse ears (within the pharmaceutical carrier Me_2CO) to

Me_2CO) to assess skin irritation - i.e., redness of the skin (please note that it is notoriously well recognized in the art that mouse ear assays are employed so as to show inflammation caused by the irritant administered therein, and that inflammation reads upon immune system stimulation as evidenced by Benjamini et al. because inflammation is a stimulation of phagocytosis which is part of the body's innate/natural immune response - see pages 15-18 of Benjamini et al.) - see entire documents (please also note that the claims are in no way limited to administering an isolated compound of the elected species, as the instant claims only recite administering such a compound and thus, they read upon administering a milk extract containing such a compound; nor are the claims limited to administering the compound to a particular type of subject). The various claimed functional effects would be inherent to the reference angeloyl-substituted ingenane compounds and derivatives thereof.

Therefore, each of the cited references is deemed to anticipate the instant claims above.

Claims 33, 34, 74-77, and 83-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Hecker et al. (US 4,716,179).

Hecker et al. teach administering an antineoplastic composition which comprises an effective amount of a non-irritating or slightly irritating compound obtained from a *Euphorbia* plant including one of various ingenane compounds and derivatives thereof (which also read upon an "angeloyl-substituted ingenane derivative" - see U.S.C. 112, second paragraph rejection above with respect to the term "derivative") - see entire document including col 1, line 12 - col 2,

line 45; col 7, lines 4-8; col 8, Ex 3-records 1 and 2; col 9, Ex 4). The various claimed functional effects, including *in vivo* stimulation of the immune response, would be inherent to the reference compound derivatives.

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 U.S.C. § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33, 34, 74-77, and 83-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Tamas (EP 330094).

Tamas teaches treating malignant and non-malignant tumors such as breast and lung cancer using an ethanolic extract of *Euphorbia hirta* (see entire document including English abstract). Please note that someone suffering from malignant and non-malignant tumors would

intrinsically be a subject in need of immune system stimulation so as to help their body fight the growth of the malignant and non-malignant cells. As the specification (as well as claim 33) disclose that the claimed compound can be derived from *Euphorbia hirta* - e.g., via ethanol extraction - the claimed compound would inherently be present within the reference ethanol extract (please note that the claims are in no way limited to administering an isolated compound of the elected species, as the instant claims only recite administering such a compound and thus, they read upon administering an ethanolic extract containing such a compound; nor are the claims limited to administering the compound to a particular type of subject). Consequently, the reference appears to anticipate the instant claims above.

However, even if the referenced method and the claimed method are not one and the same and there is, in fact, no anticipation, the referenced method would have rendered the claimed method obvious to one of ordinary skill in the art at the time the claimed invention was made in view of the clear close relationship between the *in vivo* use a compound extracted from a *Euphorbia* plant of the same genus and species. The various claimed functional effects, including *in vivo* stimulation of the immune system, would be intrinsic to such an ethanolic extract.

Accordingly, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated by the reference, especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claim Rejections - 35 U.S.C. § 103

Claims 33, 34, 74-77, and 82-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hecker et al. (US 4,716,179).

Hecker et al. teach treating a solid tumor via administering an antineoplastic composition which comprises an effective amount of a non-irritating or slightly irritating compound obtained from a *Euphorbia* plant including one of various ingenane compounds and derivatives thereof (which also read upon an "angeloyl-substituted ingenane derivative" - see U.S.C. 112, second paragraph rejection above with respect to the term "derivative") - see entire document including col 1, line 12 - col 2, line 45; col 7, lines 4-8; col 8, Ex 3-records 1 and 2; col 9, Ex 4). Please note that someone suffering from cancerous tumors would intrinsically be a subject in need of immune system stimulation so as to help their body fight the cancerous cells. Hecker et al. does not expressly teach using the conventional carrier ingredients instantly claimed. However, the adjustment of particular conventional working conditions (e.g., incorporating such anti-cancer agents within a conventional pharmaceutical form using one or more conventional carrier ingredients, and/or adjusting the ethanol content of the ethanolic extract solution), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Thus, the invention as a whole is *prima facie* obvious over the reference, especially in the absence of evidence to the contrary.

Claims 33, 34, 74-77, and 82-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamas (EP 330094) and El-Merzabani et al (Planta Med., 1979 - this reference was provided in parent Application No. 09/486,199).

Tamas et al. is relied upon for the reasons discussed *supra*.

El-Merzabani et al. teach a cytotoxic ethanolic extract of *Euphorbia peplus* which beneficially displays some anti-tumor activity (see entire document including pages 150-153 including Table 1). As the specification (as well as claim 33) disclose that the claimed compound can be derived from *Euphorbia peplus* - e.g., via ethanol extraction - the claimed compound would intrinsically be present within the reference ethanol extract (again, please note that the claims are in no way limited to administering an isolated compound of the elected species, as the instant claims only recite administering such a compound and thus, they read upon administering an ethanolic extract containing such a compound; nor are the claims limited to a administering the compound to a particular type of subject).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to administer an ethanolic extract from either of the reference *Euphorbia* plant species to a subject suffering from a cancer based upon the anti-cancer activity such ethanolic extracts were shown to provide as beneficially disclosed by the cited references. Again, please note that someone suffering from cancerous tumors would intrinsically be a subject in need of immune system stimulation so as to help their body fight the cancerous cells. The adjustment of particular conventional working conditions (e.g., incorporating such anti-cancer

agents within a conventional pharmaceutical form using one or more conventional carrier ingredients, administering such anti-cancer agents to a subject suffering from a particular type of tumorous or non-tumorous cancer, and/or adjusting the ethanol content of the ethanolic extract solution), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. The various claimed functional effects, including *in vivo* stimulation of the immune system, would be intrinsic to such ethanolic extracts.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher R. Tate whose telephone number is (703) 305-7114. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached at (703) 306-3220. The Group receptionist may be reached at (703) 308-0196. The fax number for art unit 1654 is (703) 872-9306.

Christopher R. Tate,
Primary Examiner, Group 1654